DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6006

August 13, 2002

CERTIFIED MAIL –
RETURN RECEIPT REQUESTED

George Burke
President and Chief Executive Officer
Sharp
23 Carland Road
Conshohocken, Pa. 19428

WARNING LETTER

02-NWJ-28

Dear Mr. Burke:

During an inspection of your firm, Sharp, located at 147 Clinton Road, West Caldwell, N.J. between June 6, 2002 – June 14, 2002, investigators from the Food and Drug Administration (FDA) documented significant deviations from current good manufacturing practice for finished pharmaceuticals (CGMP's). See 21 CFR parts 210 and 211. These finished pharmaceutical packing deviations cause two of your products, [redacted] and [redacted] to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

The inspection revealed the following significant deficiencies:

1. Your firm failed to adequately maintain the packaging equipment used for [redacted]ots 11906B (packaging start date of November 15, 2001) and 12290B (packaging start date of December 13, 2001) in order to prevent contamination from black particles that could alter the safety, identity, strength, quality or purity of the drug product as required by 21 CFR 211.67(a). Your firm's investigation found black particles in the product, which could have resulted from the wear of the butterfly valve gaskets during primary packaging.

2. Your Quality Control Unit failed to reject case 634 that contained Lot [redacted] (packaged from November 14, 2001 to November 20, 2001) of [redacted] which did not bear the lot numbers or expiration dates, as required by 21 CFR 211.22(a). See also 21 CFR 211.130(c). Your Quality Control Inspector failed to document the missing code numbers; however, the customer issued a complaint dated 2/18/02 stating that the codes were missing.

3. At the time of the inspection, your firm had failed to conduct sufficiently thorough investigations of certain specific failures and discrepancies in the packaging process. Under 21 CFR 211.192, investigations must extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

   A) The packaging of lot 11096B ([redacted]) started on November 15, 2001, where a mechanic discovered black particles in a nozzle during primary packaging. The black particles were not retained for analysis, the Quality Control Inspector did not issue any rejection report for the black particles discovered by the mechanic, and investigation AV2002-01 (dated 1/16/02) for lot 11906B was not extended to other batches packed on the same equipment from February 28, 2001, until the time of this incident.

   B) Investigations AV2002-01 ([redacted] dated January 16, 2002) for lot 11906B, and AV2002-02 ([redacted] dated January 16, 2002) for lot 12290B document a visual inspection for the removal of black particles present in the finished products only. A total of fifty one packages were found to have black particles for lot 12290B. A partial lot rejection was documented for lot 12290B based on a visual examination, and the possible wear of the butterfly gasket that comes into contact with the product. You did not conduct the testing necessary to determine the precise cause of the black particles, i.e., why the product caused the butterfly gasket to deteriorate, or the extent to which the product had been compromised.

   Although you concede in your response dated June 25, 2002, that visual inspection was inadequate to ensure complete removal of the black particles from the finished product for lot 12290B, you justify the release of portions of the lot on the ground that your method used for black particles, visual inspection, could not "guarantee" removal of these particles in the release . Under such circumstances, you must conduct the additional testing necessary to assure that any portion of a lot to be released has not been compromised.

   C) Investigation [redacted] dated February 18, 2002 for [redacted] documents the operator's failure to restart the lot number and expiration date printer, which failure resulted in missing lot numbers and expiration dates. However, you stated to the FDA investigators that the cause of this incident was actually the operator's failure to remove defective product from the line after the film machine jammed. In addition, the investigation

does not document the number of units that were affected from the film jam at the time of this inspection, nor is there any indication in the record that your firm attempted to obtain this information from the customer who complained of the missing lot numbers and expiration dates.

4. Contrary to the requirements of 21 CFR 211.67, your firm has not demonstrated that the cleaning procedures for removing product residuals and detergents from non-dedicated packaging equipment are effective.

   A) Your firm routinely uses water to swab, regardless of the drug residue solubility. Your machine cleaning and sanitization validation protocol for [redacted] dated March 31, 1999, documents swabs being moistened with de-ionized water to remove residual active ingredient from packaging equipment after cleaning. The laboratory report for [redacted] dated April 22, 1999 documents that the swab recovery could not be performed because the active ingredient is not soluble in water. The actual level of residual active present after equipment cleaning could not be determined.

   B) The machine cleaning and sanitization validation protocol for [redacted] (dated February 27, 1998) documents that the detergent analysis sample was not collected and therefore no results are available for the level of residual detergent after the packaging equipment is cleaned.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and on the Form FDA483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems within your establishment's quality and packaging systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. Federal agencies are advised of the issuance of all Warning Letters so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to correct these deviations promptly may result in regulatory action being initiated by the FDA without further informal notice to you. These actions include, but are not limited to, seizure and/or injunction.

We have received the written responses from your firm dated June 25, 2002, July 2, 2002, and July 31, 2002. Your responses also do not provide sufficient detail for us to evaluate whether the referenced corrective actions are adequate. As a result, in order to complete our review, we will need more documentation of your corrective actions as follows:

- your firm's written procedures for conducting investigations when specific failures or discrepancies in the packaging process occur;
- documentation of the corrective action you have taken to prevent recurrence of missing lot numbers and expiration dates on [redacted]
- written procedures for cleaning non-dedicated packaging equipment that address the concerns listed above at paragraph 4; and
- any other documentation you have to demonstrate that adequate quality and packaging systems are in place, including evaluations of the employees performing quality control and packaging at your firm.

Please notify this office in writing within fifteen working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. Your response should be directed to the New Jersey District, FDA, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attn: Robert J. Maffei, Compliance Officer.

Sincerely,

Douglas I. Ellsworth
District Director
New Jersey District

cc: Daniel D. Dwyer
Sharp
Vice President of Operations
147 Clinton Road
West Caldwell, NJ, 07006